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Leading articles

Chemotherapy for 'exotic' RNA viruses

Much of the antiviral research to date has focused on commercially exploitable drugs against herpes, influenza and rhinoviruses. The list of potential antiviral agents against these viruses is actively growing (Galasso, 1981; De Clercq, 1982) and includes acyclovir, adenine arabinoside, amantadine, E-5(2-bromovinyl)-2'-deoxyuridine and rimantadine. There are other less common viruses that pose significant health problems in sufficient numbers of people also to merit the development of antiviral agents. The viruses of the toga-, bunya-, and arenaviridae families, often considered to be 'exotic' tropical viruses, are now beginning to receive special attention. Many of these 'exotic' viruses have documented epidemic potential, and are presently associated with a significant incidence of human disease. These viruses include the aetiological agents of dengue fever, Rift valley fever, and Lassa fever, plus a long list of other viruses causing encephalitis and haemorrhagic fevers in both tropical and temperate climates.

Vaccines with the notable exception of yellow fever have not been developed for most of the 'exotic' virus diseases. Even when effective vaccines are available, reliance on vaccination to provide uniform protection has proved unreliable. Immunization of entire populations of susceptible individuals is technically difficult and economically impractical, especially if attempted in the course of a developing epidemic. A recent example of this was the 1979 outbreak of yellow fever in the Gambia which occurred in a population which remained largely susceptible despite the ready availability of a safe and efficacious vaccine. Hence, the availability of vaccines does not preclude the need for effective therapeutic antiviral agents for 'exotic' viruses of far more common RNA viruses such as respiratory syncytial and parainfluenza viruses.

In-vitro screening programmes have identified a number of compounds with broad-spectrum antiviral activity against 'exotic' RNA viruses. Among these, ribavirin has been the most extensively evaluated in man and

experimental animals. It has been found to be effective against Rift valley fever, Lassa fever and the haemorrhagic phase of Machupo virus infections of monkeys (Huggins *et al.*, 1984).

For treatment of life-threatening Lassa fever, intravenous ribavirin has been used in Sierra Leone where it reduced mortality among severely ill hospitalized patients by more than 50% (McCormick, 1984).

The relative inability of ribavirin to cross the blood brain barrier makes this compound ineffective against encephalitic viral diseases although it shows good *in-vitro* activity against representative viruses such as the agents of Venezuelan and western equine and Japanese encephalitis. Attempts to improve the lipid solubility of ribavirin by adding lipophilic side chains have been essentially ineffective. Yet other possibilities exist for synthesizing a derivative which will efficiently cross the blood brain barrier. Targeting of antiviral agents to specific tissue sites has already been shown to improve the overall efficacy of compounds. For example, when ribavirin is encapsulated in liposomes a smaller dose is required for efficacy against Rift valley fever infection in mice. The use of other delivery and targeting systems such as polysaccharides, antibodies and slow-releasing copolymers need to be applied to antiviral agents.

Passive immunization, with convalescent plasma or immunoglobulin preparations, is routinely employed for both prophylaxis and treatment of many viral diseases, including hepatitis B, measles, polio, rabies, varicella and cytomegaloviruses (Levin *et al.*, 1981; Condie & O'Reilly, 1984). For treatment of some of the more exotic viral infections, this approach has had variable success. Immune plasma is difficult and expensive to collect, maintain and administer, especially in countries with limited health resources. Hence the availability of effective antiviral drugs that are inexpensive to produce and maintain would be preferable. However, for some viral infections, such as the arenavirus Junin, (the aetiological agent of Argentine haemorrhagic fever), passive immunization is clearly beneficial, and is presently the treatment of choice (Maiztegui,

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1979). For treatment of Lassa fever patients, this approach is also routinely used, although with far less convincing success, in part due to the low neutralizing antibody titres generally obtained in Lassa fever-immune plasma (Jahrling *et al.*, 1984). However, the combination of Lassa fever-immune plasma and ribavirin has been dramatically effective in treatment of monkeys experimentally infected with Lassa virus, even when treatment was delayed until late in the disease course (Jahrling, Peters & Stephen, 1984). On this basis, high-risk human Lassa fever patients in Sierra Leone are currently being treated with a combination of ribavirin plus immune plasma with encouraging results.

Interest in combination chemotherapy also has recently increased. Combinations of ribavirin and arabinofuranosyladenine (ara-A) exhibit significant synergy against types 1 and 2 herpes viruses (Allen *et al.*, 1982), while ribavirin in combination with amantadine is more effective against influenza infection in tissue culture as well as mice (Wilson *et al.*, 1982). More recently synergistic antiviral effects against RNA viruses have been found for combinations of ribavirin with either of two novel nucleotides, tiazofurin and selenazole (Huggins, Robins & Canonico, 1984). Synergistic effects have been also found for human interferon given in combination with amantadine or rimantadine against a variety of 'exotic' viruses *in vitro*. Equally promising is the synergistic antiviral effects observed between human alpha and gamma interferons (Czarniecki *et al.*, 1984; Luscri *et al.*, 1984). The potentiation of antiviral activity between different interferons offer a rational optimism for the use of combination of interferon preparations.

Finally, the number of natural products which nonspecifically activate macrophages, resulting in enhanced host resistance to viral infections, is growing. Compounds, such as glucan, muramyl di- and tripeptides, lipoidal diamine, and pyran, protect experimental animals against a variety of viral infections (Budzko, Casals & Waksman, 1978; Chang, 1984; Gangemi *et al.*, 1983; Levy & Riley 1983; Reynolds *et al.*, 1980). The specific delivery of muramyl tripeptide to liver macrophages by encapsulation in liposomes protects mice against Rift valley fever virus infection even when administered therapeutically 5 days after infection (Kende *et al.*, 1983).

The progress made to date in the development of drugs, biological response modifiers including interferons, combination chemotherapy and drug delivery promises that effective

treatments will be forthcoming and assures a place for chemotherapy in the treatment of life-threatening viral diseases.

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